Retrovirology

Poster presentation

P09-07. Balancing reversion of CTL and neutralizing antibody escape mutations within HIV-1 Env upon transmission

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Background

Many calls have been made for vaccines that induce both CTL and Nab but why this would be substantially more effective, nor the path to achieve this, are unclear. HIV-1 Env is the only protein subject to both NAb and CTL pressure. We hypothesized that serially escaping both Env-specific CTL and NAb responses could have implications for both viral fitness and the reversion of multiple mutations upon transmission to naive hosts.

Methods

The impact and reversion of 3 well-define HIV-1 Env CTL escape mutant SHIVmn229 viruses to wild-type following *in vivo* passage experiments was studied in 6 pigtail macaques. Through extensive sequencing we analyzed the relationship between the reversion of CTL mutations with adjacent N-linked glycosylation site (NLGS) mutations. Env-pseudotype viruses were constructed expressing combinations of WT and EM mutations at both CTL and NLGS sites and assessed for their susceptibility to autologous Nab in sera.

Results

Env CTL mutations either did not revert to wild type or only transiently reverted 5–7 weeks after infection. CTL escape mutant reversion was however coincident, on precisely the same viral clones, with loss of adjacent NLGS mutations, suggesting strong clonal links at viruses adapting to both immune pressures. At one site studied in detail, both CTL and NLGS mutations were needed to confer Nab early escape, with the NLGS mutations alone insufficient to confer full Nab escape.

Conclusion

We conclude CTL and NAb escape within Env can be tightly linked, reflecting remarkably flexibility in viral adaptation to multiple coincident immune pressures. Although fitness costs of individual Env-specific CTL and Nab escape mutations may not be substantial, we speculate that there may yet be opportunities to identify and target linked combinations of cellular and humoral immunity to Env that are more difficult to simultaneously escape without substantial fitness costs.